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Shylasree TS, Bryant A, Athavale R

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[Intervention Review]

Chemotherapy and/or radiotherapy in combination with surgery for ovarian carcinosarcoma

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ABSTRACT

Background

Ovarian carcinosarcoma, also known as malignant mixed Mullerian tumour, is a rare malignant gynaecological tumour constituting about 1% or less of all ovarian cancers. In over 80% of cases, there is extra-ovarian intra-abdominal spread at diagnosis. The primary treatment has traditionally been surgical cytoreduction followed by radiotherapy and chemotherapy or chemotherapy alone. Regimes have included cisplatin alone; a combination of doxorubicin, ifosfamide, dacarbazine, cyclophosphamide, taxol; and various other combinations. The effectiveness of these various regimens appears to be mixed. Therefore, there is a need to clarify if there is an optimum neoadjuvant or adjuvant therapy after surgical cytoreduction for this rare tumour. Also, it is important to address quality of life (QoL) issues related to treatment, particularly toxicity, as the overall prognosis appears to be poor.

Objectives

To assess the effectiveness and safety of various adjuvant and neoadjuvant chemotherapy and radiotherapy options or chemotherapy alone in combination with surgery in the management of ovarian carcinosarcoma.

Search methods

We searched the Cochrane Gynaecological Cancer Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE up to February 2012. We also searched registers of clinical trials, abstracts of scientific meetings, reference lists of review articles and contacted experts in the field.

Selection criteria

We searched for randomised controlled trials (RCTs) that compared neoadjuvant or adjuvant chemotherapy and radiotherapy, or chemotherapy alone, in women with ovarian carcinosarcoma (malignant mixed Mullerian sarcoma of the ovary). We also reviewed non-randomised studies (NRS) for discussion in the absence of RCTs.

Data collection and analysis

Two review authors independently assessed whether potentially relevant studies met the inclusion criteria. No trials were found and therefore no data were analysed.

Main results

The search strategy identified 297 unique references of which all were excluded.

Authors' conclusions

We found no evidence to inform decisions about neoadjuvant and adjuvant chemotherapy and radiotherapy regimens, or chemotherapy alone, for women with ovarian carcinosarcoma. Ideally, an RCT that is multicentre or multinational, or well designed non-randomised studies that use multivariate analysis to adjust for baseline imbalances, are needed to compare treatment modalities and improve current knowledge. Further research in genetic and molecular signalling pathways might improve understanding of this tumour subtype.

PLAIN LANGUAGE SUMMARY

Chemotherapy, radiotherapy or both after surgery for treatment of a rare tumour of the ovary

Ovarian carcinosarcoma (malignant mixed Mullerian tumour) is a rare malignant gynaecological tumour comprising around 1% or less of all ovarian cancers. These tumours contain both carcinomatous (arising from the epithelial tissue, the tissue that lines the cavities and surfaces of structures throughout the body) and sarcomatous tissue (arising from the connective tissue) within them. This tumour usually presents at an advanced stage and has a poor survival rate despite treatment. It is usually treated with a combination of surgery and chemotherapy, and sometimes radiotherapy. Various types of chemotherapy drugs have been used to treat the woman before and after surgery (neoadjuvant and adjuvant settings).

There is currently no evidence to determine whether any form of chemotherapy or radiotherapy, or both, in combination with surgery is better or worse for prolonging survival and improving quality of life or toxicity. The review highlights the need for good quality studies comparing various chemotherapy regimens, both pre- and post-surgery, with or without radiotherapy. Multicentre, multinational and collaborative good quality studies are needed to investigate this rare disease.

BACKGROUND

Description of the condition

Ovarian carcinosarcoma is a rare malignant gynaecological tumour comprising around 1% or less of all ovarian carcinomas (Russell 1992). Ovarian carcinosarcomas differ from epithelial ovarian tumours in that they contain both carcinomatous (arising from the epithelial tissue, which lines the cavities and surfaces of structures throughout the body) and sarcomatous (mesenchymal, arising from the connective tissue) tissue. The histology of the carcinomatous components is similar to conventional epithelial ovarian carcinoma (serous, endometroid etc.). The sarcomatous component can arise from or resemble the mesenchymal tissue of the ovary (homologous) or can be different to the mesenchymal tissue of the ovary and resemble that found in extra-ovarian sites (heterologous). Special immunohistochemical staining (an investigative tool that provides supplemental information to the routine morphological assessment of tissues) helps in confirming the subtypes mentioned above (George 1991). There are various hypotheses which have been examined to explain the presence of carcinomatous and sarcomatous cell types within this tumour. The combination theory suggests that a common stem cell (cell which is capable of giving rise to all cell types) gives rise to both the epithelial and mesenchymal components (Guarino 1998; Jin 2003; Sonoda 2000); the conversion theory suggests an origin from a common epithelial clone and an epithelial-to-mesenchymal transformation-based mechanism (otherwise called epithelial de-differentiation) (Guarino 1998; Schipf 2008). In over 80% of cases, there is extra-ovarian intra-abdominal spread at diagnosis (Russell 1992). The diagnosis is confirmed by histology with the presence of malignant epithelial and mesenchymal components. The standard International Federation of Gynaecology and Obstetrics (FIGO) staging for ovarian epithelial tumour is applied to ovarian carcinosarcoma (Benedet 2000) and the prognosis is generally poor (Ariyoshi 2000; Hanjani 1983).

Description of the intervention

The primary treatment has traditionally been surgical cytoreduction (surgery attempting to remove as much of the tumour as possible) followed by radiotherapy and chemotherapy (Carlson 1983; Chang 1995) or chemotherapy alone (Bicher 1995). Treatment guidelines are extrapolated from epithelial ovarian carcinoma. Due to the rarity of this tumour, chemotherapy regimes have often changed over the course of time (Brown 2004). Optimal cytoreduction followed by adjuvant platinum-based chemotherapy has been practiced based on case series and prospective trials (Morrow 1986; Sutton 1994; Tate Thigpen 2004). Combination platinum chemotherapy in combination with paclitaxel, doxorubicin, ifosfamide and other agents has been used with varying response rates (Duska 2002; Morrow 1986; Prendiville 1994; Simon 1991). The results of these various regimens appear to be mixed.

Why it is important to do this review

A review of published cases indicated a high one-year mortality rate of 78% (Hanjani 1983) in this rare tumour irrespective of stage. A more recent publication suggested 40% survival at one year (Harris 2003). Advanced surgical stage did not affect the median overall survival (OS) in one study (Terada 1989), but was associated with a poor prognosis in a more recent study (Ariyoshi 2000). More recent studies have indicated that median survival could be improved with platinum-based chemotherapy (Bicher 1995; Duska 2002). One of the largest reported data series of 47 cases over 10 years (Harris 2003) indicates that maintaining consistency in treatment plans is difficult and the tumour remains more aggressive than epithelial ovarian cancer (Barnholtz-Sloan 2004). A case series which compared carcinosarcoma of the ovary with epithelial carcinoma of the ovary showed an inferior response with platinum-based chemotherapy in the former group (Brown 2004). There is, therefore, a need to clarify if there is an optimum therapy after surgical cytoreduction or in the neoadjuvant setting for this rare tumour. Also, it is important to address quality of life (QoL) issues related to treatment, particularly toxicity related to treatment, as the overall prognosis appears to be poor.

OBJECTIVES

To assess the effectiveness and safety of chemotherapy (both adjuvant and neoadjuvant) regimens, with or without radiotherapy, in combination with surgery in the management of ovarian carcinosarcoma (malignant mixed Mullerian tumour).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women of any age with a diagnosis of ovarian carcinosarcoma (malignant mixed Mullerian tumour of the ovary) at any FIGO stage.

Types of interventions

Interventions

We considered direct comparisons between any of the following interventions:

- adjuvant chemotherapy with or without radiotherapy (surgery followed by chemotherapy with or without radiotherapy);
- adjuvant radiotherapy and combination chemotherapy;
- adjuvant single drug chemotherapy versus combination chemotherapy;
- neoadjuvant chemotherapy and radiotherapy (chemotherapy with or without radiotherapy followed by surgery).

Additionally, we considered any of the above interventions in comparison with the following:

- surgery alone.

Types of outcome measures

Primary outcomes

- Overall survival (OS), survival until death from all causes (survival from the time when women were randomised)
- Disease-free survival (DFS), defined as time to recurrence

Secondary outcomes

1. Quality of life (QoL), measured using a scale that has been validated through reporting of norms in a peer-reviewed publication.
2. Cost effectiveness.
3. Adverse events classified according to CTCAE 2006:
   a. direct surgical morbidity, death within 30 days, haemorrhage (intraoperative and postoperative), intraoperative organ injury (bladder, ureter, bowel and vessels etc.), febrile morbidity and postoperative site specific infection (surgical site, pelvic, urinary, bowel), postoperative complications related to the urinary and gastrointestinal (GI) tract (obstruction, fistulae, incontinence), unexpected return to theatre, delayed discharge due to complication,
   b. surgical related systemic morbidity, vascular and thromboembolic (thrombosis, embolism, coagulopathy), pulmonary (infection, atelectesis etc.), lymphatics (lymphaedema, lymphocele), metabolic (diabetic complications, renal failure etc.), cardiac events (cardiac ischaemia, failure), hepatobiliary, cerebrovascular accidents, sexual dysfunction, chronic pain and psychological morbidity,
   c. radiotherapy toxicity,
   d. chemotherapy toxicity.

Grades of toxicity relating to radiotherapy and chemotherapy were extracted and grouped as:

a. haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage),
b. gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis),
c. genitourinary (cystitis, incontinence),
d. skin (stomatitis, mucositis, alopecia, allergy),
e. neurological (peripheral and central),
f. pulmonary,
g. lymphatics (lymphocele, lymphedema),
h. psychosexual,
i. other.

Search methods for identification of studies

Papers in all languages were sought and translations carried out when necessary.

Electronic searches

The following electronic databases were searched:

- Cochrane Gynaecological Cancer Review Group Trials Register,
- Cochrane Central Register of Controlled Trials (CENTRAL) issue 2, 2012,
- MEDLINE (to February 2012),
- EMBASE (to February 2012).

The CENTRAL, MEDLINE and EMBASE search strategies based on terms related to the review topic are presented in Appendix 1, Appendix 2 and Appendix 3 respectively.

Databases were searched from 1950 until February 2012.

All relevant articles found were identified on PubMed and, using the 'related articles' feature, a further search was carried out for newly published articles.

Searching other resources

Unpublished and grey literature

Metaregister, Physicians Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and Gynaecologic Oncologists of Canada (http://www.g-o-c.org) were searched for ongoing trials.

Handsearching

Reports of conferences were handsearched in the following sources:

- Gynecologic Oncology (Annual Meeting of the American Society of Gynecologic Oncologists),
- International Journal of Gynecological Cancer (Annual Meeting of the International Gynecologic Cancer Society),
- British Journal of Cancer,
- British Gynaecological Cancer Society (BGCS),
- British Cancer Research Meeting,
- Annual Meeting of European Society of Medical Oncology (ESMO),
- Annual Meeting of the American Society of Clinical Oncology (ASCO),
- BioMed (open text publisher),
- American Association for Cancer Research (AACR) conferences,
- European Society of Gynaecological Oncology (ESGO) conference.

We additionally searched the Journal of Ovarian Research: http://www.ovarianresearch.com/home/.

Data collection and analysis

Selection of studies

Two review authors (TS or RA and AB) downloaded all the titles and abstracts retrieved by electronic searching to the reference management database EndNote, duplicates were removed and the titles and abstracts of the remaining references were examined independently. There were a number of case reports and retrospective studies on interventions (mainly combination chemotherapy) for ovarian carcinosarcoma however none was of sufficient quality or appeared to use statistical adjustment to minimise selection bias, so we did not alter our inclusion criteria to accommodate non-randomised studies (NRS) (see Agreements and disagreements with other studies or reviews for details of these studies). All were excluded at this stage as they clearly did not meet the inclusion criteria. We did not identify any ongoing RCTs which met our inclusion criteria from our searches of the grey literature. In future updates of the review, we will employ the methods found in the Differences between protocol and review.

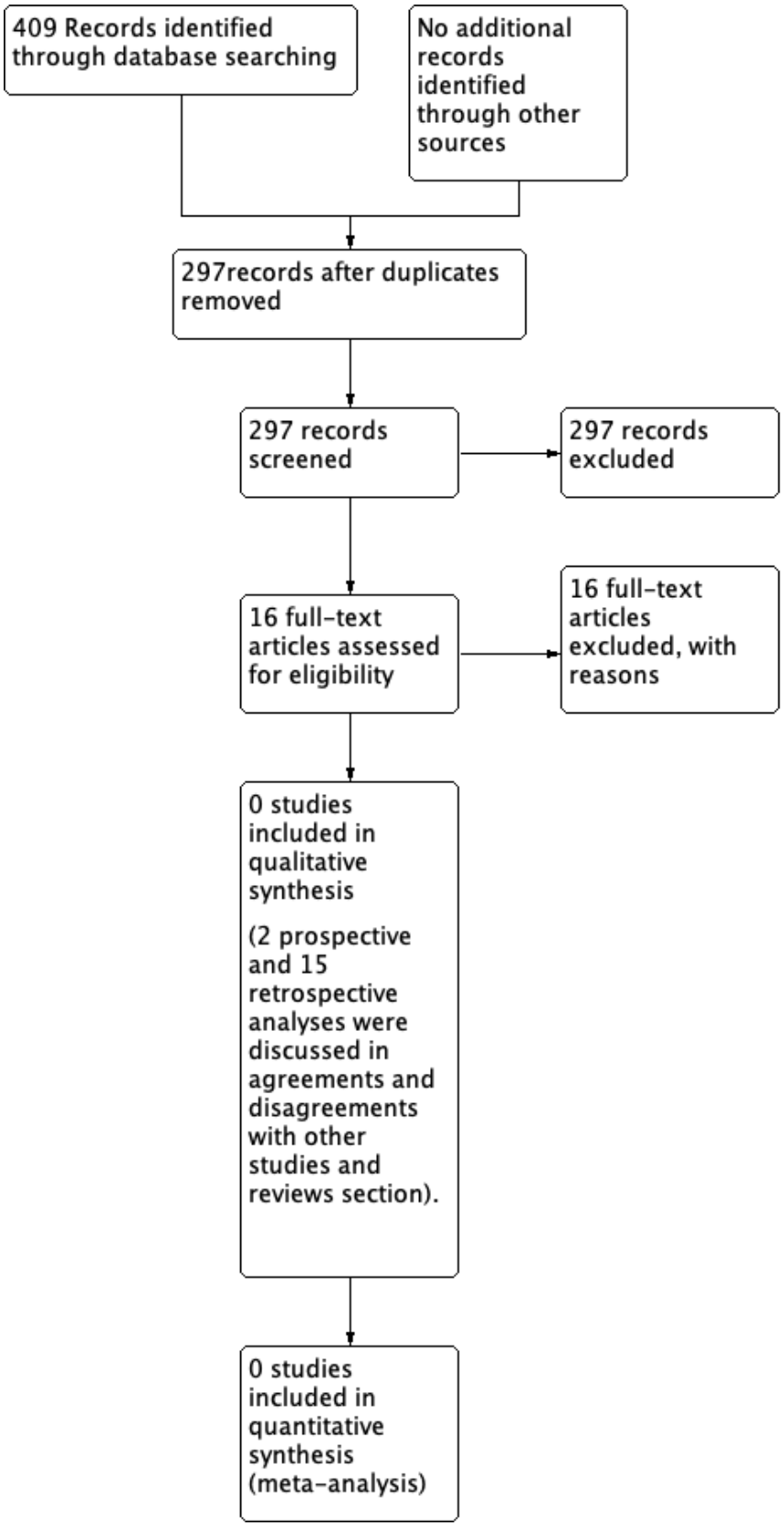
RESULTS

Description of studies

Results of the search

The search strategy identified 186 references in MEDLINE, 207 in EMBASE, 13 in CENTRAL and three in the Specialised Register. When the search results were merged into EndNote and duplicates were removed there were 297 unique references. The abstracts of these were read independently by two review authors and all were excluded (Figure 1).

Figure 1. PRISMA 2009 flow diagram.



Two review authors (RA and AB) independently searched the grey literature; these searches also did not identify any relevant studies.

Risk of bias in included studies

No trials were found and therefore the risk of bias tool was not applied.

Effects of interventions

No data were available.

DISCUSSION

Summary of main results

We did not identify any trials that compared the effectiveness and safety of neoadjuvant or adjuvant chemotherapy with or without radiotherapy in combination with surgery for women with ovarian carcinosarcoma. Therefore, there is currently no evidence to determine whether any form of chemotherapy, with or without radiotherapy, in combination with surgery is better or worse in terms of prolonging survival, QoL or toxicity.

We specified OS and DFS as the primary outcomes of interest. Quality of life should perhaps be the main focus if future trials are conducted since treatment related morbidity is likely to degrade the quality of the time that women live. This is especially important in women with ovarian carcinosarcoma where a number of retrospective studies and case reports have shown very poor survival rates (Andersen 1989; Brown 2004).

Quality of the evidence

No studies met the inclusion criteria for this review, so there is no evidence to assess.

Potential biases in the review process

Two review authors independently carried out a comprehensive search, including a thorough search of the grey literature, and all references were sifted. We were restrictive in our inclusion criteria with regards to types of studies as we planned to only include RCTs, as we suspected that some of the NRS designs were dubious and would have been prone to selection bias. No relevant NRSs appeared to use appropriate statistical adjustment or were of adequate quality. Therefore, we attempted to ensure that we did not overlook any relevant evidence by searching a wide range of sources and ensuring the review was not based on poor quality evidence by excluding case reports and poor quality retrospective studies. We felt it was better to highlight the need for RCTs, or at the very least good quality NRSs, rather than report the results of low quality studies that are very likely to be misleading.

The greatest threat to the validity of the review is likely to be publication bias, that is studies that did not find the treatment to have been effective may not have been published. We were unable to assess this possibility as we did not find any studies that met the inclusion criteria.

Agreements and disagreements with other studies or reviews

Two prospective Gynecologic Oncology Group (GOG) studies looked at the outcomes of women diagnosed with ovarian carcinosarcoma, but these studies included too few women in order to make reliable comparisons (Morrow 1986; Tate Thigpen 2004).

Morrow 1986 registered 15 women with a diagnosis of ovarian carcinosarcoma who were treated with combinations of surgery, chemotherapy and radiotherapy depending on the stage of the disease. A combination of vincristine, dactinomycin and cyclophosphamide was used in some women. Survival was better in women with early stage disease or with a smaller residual tumour volume.

Tate Thigpen 2004 studied the cytotoxic effect of platinum in women diagnosed with ovarian carcinosarcoma. The median progression-free interval was 5.2 months and the median OS was 11.7 months (n = 130). Forty-four women were evaluable for response and showed an overall response of 20%. Survival was favourable for women with non-measurable disease and also in women who responded to platinum. Adverse effects were not uncommon. We agree that this is one of the largest prospective series of women with carcinosarcoma ovary studied so far. The recruitment took 20 years, which makes it difficult to compare various cytotoxic drugs along with platinum. Despite the platinum response being similar to uterine carcinosarcoma, it is still lower than the conventional epithelial ovarian tumours, which means that platinum alone as a cytotoxic drug may not be effective in improving survival in ovarian carcinosarcoma. This was confirmed by Brown 2004 who compared epithelial ovarian tumours with carcinosarcoma of the ovary in their retrospective case series and found an inferior response to platinum-based chemotherapy in the carcinosarcoma group.

A recent case-control study (Rauh-Hain 2011) reviewed 50 cases of ovarian carcinosarcoma of the ovary, each case was matched to two women with serous ovarian epithelial carcinoma. Shorter time to recurrence, increased platinum resistance, poorer prognosis with suboptimal cytoreduction and poorer OS were noticed in women with ovarian carcinosarcoma compared to serous epithelial ovarian cancer. Jonson 2006 looked at 17 cases of ovarian carcinosarcoma and 87 women with uterine carcinosarcoma and found no difference in survival between the two groups.

The Chun KC, Cicen 2008 and Duska 2002 studies reported a retrospective analysis of 40, 26 and 28 women diagnosed with ovarian carcinosarcoma, respectively, and showed improved survival with optimal debulking and platinum-based combination treatment. A platinum combination with taxanes was used in two studies (Chun KC; Duska 2002) and a combination of platinum and Ifosfamide was used in the Cicen 2008 study. Recruitment took 15 to 20 years with various chemotherapeutic agents being used over that period of time, which makes it difficult to compare various regimens. A retrospective series of 31 women (Rutledge 2006) showed improved survival with optimal debulking and the use of ifosfamide and cisplatin chemotherapy compared to a carboplatin and taxol combination. The median OS was 21 months for the whole group.

Signorelli 2009 reviewed 41 women with ovarian carcinosarcoma over a period of 11 years. The women underwent surgery and were given platinum-based combination chemotherapy. The overall survival was 20 months. The response to the platinum-based combination (anthracycline, alkylating agent) was good but was associated with high toxicity and the numbers in the two chemotherapeutic regimens were small. Prendiville 1994 reported

a series of 20 women over a 10-year period. The analysis showed a median survival of 14 months and suggested that platinum and cyclophosphamide may be useful therapy following surgery. Chang 1995 studied 37 women with ovarian carcinosarcoma and found stage to be an independent prognostic factor and single agent platinum to be effective to some extent. Sutton 1994, in their phase II trial, reviewed 32 women who were previously treated with platinum-based chemotherapy for ovarian carcinosarcoma and were administered ifosfamide; they found ifosfamide to have activity.

Harris 2003 retrospectively reviewed 40 women diagnosed with ovarian carcinosarcoma. Eighty per cent presented with advanced stage disease. More than 50% had bulky disease, associated with worse prognosis, and the majority received platinum-based chemotherapy following surgery. Overall, the one- and five-year survival rates were 40% and 7.5% respectively, which is much lower than for serous epithelial ovarian carcinoma. Leiser 2007 reviewed 30 women with a diagnosis of ovarian carcinosarcoma. All the women had stage III or IV ovarian carcinosarcoma except one who had stage II disease. Fifty-seven per cent had optimal cytoreduction and all women received platinum and taxane as first-line chemotherapy. The three- and five-year survival rates were 53% and 30% respectively. Even though there was a trend towards a better response rate with optimal cytoreduction, it did not affect OS. Muntz 1995 reviewed 27 women with a diagnosis of ovarian carcinosarcoma and found advanced stage to be a significant prognostic factor. Less than 50% of women underwent optimal cytoreduction. The majority received platinum-based chemotherapy. Few women were treated with postoperative radiotherapy. There was a trend towards improved survival with optimal cytoreduction and platinum-based chemotherapy but it was difficult to interpret because of the small numbers.

All the above mentioned studies consistently confirmed that the OS is poor in women with ovarian carcinosarcoma as compared to epithelial serous ovarian carcinoma. Most studies have confirmed that platinum has some activity in this tumour type. Other variables such as suboptimal cytoreduction, feasibility for cytoreduction and increased platinum resistance have been commented upon by some studies. A major improvement in survival has not been seen in this group of women despite extrapolating cytoreduction and platinum-based combination therapy. All the above studies had inadequate or no comparison groups for various adjuvant regimens and most of the studies were retrospective case series, and hence inferences cannot be made scientifically. The difficulty in recruiting women for a prospective trial, which has limitations because of the rarity of the tumour, is obvious.

AUTHORS' CONCLUSIONS

Implications for practice

We found no current evidence to guide clinical practice with regards to various adjuvant treatment regimens in ovarian carcinosarcoma. As ovarian carcinosarcomas are considered a subgroup of ovarian epithelial tumours, they will tend to be treated similarly despite lack of good evidence.

Implications for research

To determine the effectiveness and safety of various neoadjuvant and adjuvant chemotherapy regimens, with or without radiotherapy, in combination with surgery in ovarian carcinosarcoma a RCT needs to be conducted. Preferably this should be a multicentre, multinational trial that attempts to recruit as many women as possible to increase the power of the trial given the rarity of the disease. We specified OS and DFS as the primary outcome of interest, but QoL along with survival should perhaps be the main focus if future trials are conducted as the prognosis for women with ovarian carcinosarcoma is currently poor and treatment-related morbidity is likely to degrade the quality of the time that the women live.

The Cancer Genome Atlas project has analysed various molecular aberrations that cause high grade serous ovarian epithelial carcinoma, which is important for developing and analysing targeted therapy (The Cancer Genome Atlas Research Network 2011). There are few studies which have looked at molecular abnormalities with abnormal signalling pathways in ovarian carcinosarcoma and genital tract carcinosarcoma (Costa 1996; Raji 2011; Sawada 2003). Further research in this area is critical in developing targeted therapy for this tumour subtype.

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APPENDICES

Appendix 1. CENTRAL search strategy

CENTRAL Issue 2, 2012

1. MeSH descriptor Ovarian Neoplasms explode all trees
2. ovar*
3. 1 or 2
4. MeSH descriptor Carcinosarcoma explode all trees
5. carcinosarcoma*
6. MeSH descriptor Mixed Tumor, Mullerian explode all trees
7. (mixed mullerian) and (tumo* or sarcoma*)
8. (#4 OR #5 OR #6 OR #7)
9. (#3 AND #8)
10. radiotherap*
11. Any MeSH descriptor with qualifier: RT
12. radiation
13. MeSH descriptor Radiotherapy explode all trees
14. chemotherap*
15. Any MeSH descriptor with qualifier: DT
16. MeSH descriptor Antineoplastic Agents explode all trees
17. MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
18. MeSH descriptor Chemotherapy, Adjuvant explode all trees
19. MeSH descriptor Neoadjuvant Therapy explode all trees
20. (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
21. (#9 AND #20)

Appendix 2. MEDLINE search strategy

Medline Ovid 1950 to February 2012

1. exp Ovarian Neoplasms/
2. ovar*.mp.
3. 1 or 2
4. exp Carcinosarcoma/
5. carcinosarcoma*.mp.
6. Mixed Tumor, Mullerian/
7. (mixed mullerian and (tumo* or sarcoma*)).mp.
8. 4 or 5 or 6 or 7
9. 3 and 8
10. radiotherap*.mp.
11. radiotherapy.fs.
12. radiation.mp.
13. exp Radiotherapy/
14. chemotherap*.mp.
15. drug therapy.fs.
16. exp Antineoplastic Agents/
17. Antineoplastic Combined Chemotherapy Protocols/
18. Chemotherapy, Adjuvant/
19. Neoadjuvant Therapy/
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 9 and 20

key:

mp=title, original title, abstract, name of substance word, subject heading word, unique identifier

Appendix 3. EMBASE search strategy

Embase Ovid 1980 February 2012

1. exp ovary tumor/
2. ovar*.mp.
3. 1 or 2
4. carcinosarcoma/
5. carcinosarcoma*.mp.
6. mixed Mullerian tumor/
7. (mixed mullerian and (tumo* and sarcoma*)).mp.
8. 4 or 5 or 6 or 7
9. 3 and 8
10. radiotherap*.mp.
11. rt.fs.
12. radiation.mp.
13. exp radiotherapy/
14. exp cancer radiotherapy/
15. exp adjuvant therapy/
16. chemotherap*.mp.
17. dt.fs.
18. exp antineoplastic agent/
19. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 9 and 19

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

WHAT'S NEW

Date	Event	Description
24 March 2020	Review declared as stable	No new studies identified in the most recent search - 14 October 2019. A new review will be developed in the future to include non-randomised studies.

CONTRIBUTIONS OF AUTHORS

TS, RA and AB searched for relevant trials. TS, RA and AB determined the relevance of trials for the review. AB drafted methodological and statistical sections of the review as well as various sections of the discussion. TS drafted clinical sections of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department of Health, UK.

  NHS Cochrane Collaboration programme Grant Scheme CPG-10/4001/12

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We had initially decided to run the searches with an RCT filter but ultimately ran them without as the number of hits was low. We also decided not to include NRSs when no RCTs were identified due to the problem of selection bias and the fact that no studies appeared to use satisfactory statistical adjustment for important prognostic factors. We had initially stated the following in the protocol:

"It is likely that there are no RCTs of treatment for ovarian MMT. If no such trials are identified, the search strategy will be re-run without the RCT filter so that any other papers containing prospective or retrospective data can be collated and listed in excluded studies. A systematic discussion of observational studies, case-controlled studies and studies with historic controls will be considered if no RCTs are identified."

Results of NRSs are discussed in the Agreements and disagreements with other studies or reviews section.

Selection of studies

Copies of the full text of relevant references will be obtained. Two review authors (AB, TS) will assess the eligibility of retrieved papers. We will resolve disagreements by discussion. Reasons for exclusion will be documented.

Data extraction and management

For included trials, data will be abstracted as recommended in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will extract data independently and will include:

- author, year of publication and journal citation (including language);
- country;
- setting;
- inclusion and exclusion criteria;
- study design, methodology;
- study population (participant characteristics, age, stage and postoperative residual disease);
- number of participants in each arm of the trial;
- total number of intervention groups;
- ovarian carcinosarcoma details (FIGO stage, histology, tumour grade);
- type of intervention (chemotherapy agents and radiotherapy, dosage and timing of administration relative to surgery);
- length of follow-up;
- withdrawals from treatment protocol;
- number of participants who experienced delays in treatment or received all, part or none of the proposed treatment;
- risk of bias in study (see below);
- outcomes OS, PFS, QoL and adverse events:
  * for each outcome, outcome definition,
  * unit of measurement (if relevant),
  * for scales, upper and lower limits, and whether high or low score is good,
  * results, number of participants allocated to each intervention group,
  * for each outcome of interest, sample size, missing participants.

Data on outcomes will be extracted as below

- For time to event (e.g. overall survival) data, we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports; if these are not reported, we will attempt to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. adverse events, or deaths if it was not possible to use a HR), we will extract the number of women in each treatment arm who experienced the outcome of interest and the number of women assessed at endpoint in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation of the outcome of interest and the number of women assessed at the endpoint in each treatment arm at the end of follow-up in order to estimate the mean difference (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales) between treatment arms and its standard error.

Both unadjusted and adjusted statistics will be extracted, if reported.

Where possible, all data extracted will be relevant to an intention-to-treat analysis in which participants are analysed in the groups to which they were assigned.

The time points at which outcomes were collected and reported will be noted.

Two review authors will abstract data independently onto a data abstraction form specially designed for the review. Differences between review authors will be resolved by discussion.

Assessment of risk of bias in included studies

The risk of bias in included RCTs will be assessed using the Cochrane Collaboration's tool and the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This will include an assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data, where we will code a satisfactory level of loss to follow-up for each outcome as:
  - Yes, if fewer than 20% of women are lost to follow-up and reasons for loss to follow-up were similar in both treatment arms,
  - No, if more than 20% of women are lost to follow-up or reasons for loss to follow-up differed between treatment arms,
  - Unclear, if loss to follow-up is not reported;
- selective reporting of outcomes;
- other possible sources of bias.

The risk of bias tool will be applied independently by two review authors (TS, AB) and differences will be resolved by discussion. Results will be presented in the risk of bias tables and also in both a risk of bias graph and a risk of bias summary plot. Results of the meta-analyses will be interpreted in light of the findings with respect to risk of bias.

Measures of treatment effect

We will use the following measures of the effect of treatment.

- For time to event data, we will use the HR.
- For dichotomous outcomes, we will use the RR.
- For continuous outcomes, we will use the mean difference between treatment arms (if trials measured outcomes on the same scale) or standardised mean differences (if trials measured outcomes on different scales).

Dealing with missing data

We will not impute missing outcome data for the primary outcome. If data are missing or only imputed data are reported, we will contact trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

Heterogeneity between studies will be assessed by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity (Deeks 2001) and, if possible, by subgroup analyses (see below). If there is evidence of substantial heterogeneity, the possible reasons for this will be investigated and reported.

Assessment of reporting biases

We will not assess the potential for small study effects such as the potential for publication bias because, given the rarity of ovarian carcinosarcoma, there will be an insufficient number of included studies in which to make this assessment. We did not identify any included trials from 1950 to October 2010 so future updates in the short term are unlikely to yield many trials in this area.

Data synthesis

If sufficient clinically similar studies are available, their results will be pooled in meta-analyses. Adjusted summary statistics will be used, if available; otherwise unadjusted results will be used.

- For time to event data, HRs will be pooled using the generic inverse variance facility of RevMan 5.
- For dichotomous outcomes, the RR will be calculated for each study and these will then be pooled.
- For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measured the outcome on the same scale, otherwise standardised mean differences will be pooled.

Random-effects models with inverse variance weighting will be used for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses will be performed, grouping the trials by:

- disease-free interval (DFI).

Factors such as age, stage, length of follow-up, adjusted or unadjusted analysis will be considered in the interpretation of any heterogeneity.

Sensitivity analysis

Sensitivity analyses will be performed excluding trials which did not report: (i) concealment of allocation, and (ii) blinding of the outcome assessor.

INDEX TERMS

Medical Subject Headings (MeSH)

Carcinosarcoma [*drug therapy] [*radiotherapy] [surgery]; Chemotherapy, Adjuvant [methods]; Ovarian Neoplasms [*drug therapy] [*radiotherapy] [surgery]; Radiotherapy, Adjuvant [methods]

MeSH check words

Female; Humans